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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/668,482	09/25/00	PETKOVICH	P 57600/00035

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EXAMINER	
SLOBODYANSKY, E	
ART UNIT	PAPER NUMBER
1652	8

DATE MAILED: 11/06/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/668,482	Petkovich et al.
Examiner	**Group Art Unit**
Elizabeth Slobodyansky	1652

☒ Responsive to communication(s) filed on Feb 20, 2001.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire _____ month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 83-106 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 83-106 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

This application is a divisional of application 08/882,164, now US Patent 6,306,624.

The preliminary amendment filed concurrently with the application amending the specification to insert the reference to the prior applications has been entered.

The preliminary amendment filed on February 20, 2001 canceling claims 1-82 and adding claims 83-106 has been entered.

Claims 83-106 are pending.

Specification

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825. 37 CFR 1.821(d) requires the use of assigned sequence identifier in all instances where the description or claims of a patent application discuss sequences.

The following are examples of incompliance where sequence containing more than four amino acids or ten nucleotides are given without a sequence identifier: sequences shown on pages 8 and 9.

Claim Objections

Claims 83-94 and 97-102 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

The proper recitation of the Markush group requires only a single "or" connecting the members such as SEQ ID NO:3, SEQ ID NO:5 or SEQ ID NO:31, for example.

Claims 97-102 depend from claim 96. The fragments, or epitopes, are not included in the scope of claim 96. Claim 96 requires for an antibody to be elicited by a protein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 96-106 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The newly added claims encompass all polypeptides of any function that bind to any antibody specific to for SEQ ID NO:2, SEQ ID NO:4 or SEQ ID NO:32. The Examiner is unable to locate adequate support in the specification for such polypeptides. Thus there is no indication that polypeptides encompassed by claims 96-106 were within the scope of the invention as conceived by Applicants at the time the application was filed.

Accordingly, Applicants are required to cancel the new matter in the response to this Office Action.

Claims 83, 86-90 and 93-106 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 83, 86-90, 93-95 and 103-106 recite "a conservatively substituted amino acid variant" of the amino acid sequences encoded by SEQ ID NOs: 3, 5 or 31 or encoded by a DNA that hybridizes thereto under specific conditions. This amounts to any structure having the same function as a protein encoded by SEQ ID NOs: 3, 5 or 31. The structural limitations are insufficient because while a substitution is required to be conservative any amino acid residue in the sequence can be substituted resulting in a completely novel structure that is not described. This is equivalent to a claim with no

structural limitations wherein an enzyme is defined by the function only. Furthermore, the function described only as "ability to oxidize a retinoid" encompasses many different functions.

Claims 83, 86-90 and 93-95 are included in this rejection because the function recited in the claims encompasses any oxidizing activity with substrate specificity as broad as any retinoid, i.e., retinoic acid (RA), retinal, retinol in every stereo configuration as well as undescribed natural and artificial variants thereof (see the specification, paragraph bridging pages 5 and 6). Claims 99 and 93-95 limit the enzymatic activity to hydroxylating any retinoid at the 4-position of the β-ionone ring without any limitations on the substrate specificity.

The specification discloses only a single species of the claimed genus, a retinoic acid inducible protein having all-*trans* retinoic acid 4-hydroxylase activity, which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus.

Claims 96-106 are drawn to a polypeptide that binds to an antibody specific for SEQ ID NOs: 2, 4 or 32 and has no function.

Therefore, the claims are drawn to a genus of polypeptides of any function. The genus of polypeptides that comprises these above polypeptide molecules is a large variable genus encompassing many different proteins and fragments thereof. Many functionally unrelated polypeptides are encompassed within the scope of these

claims, including partial sequences. It encompasses both a polypeptide having an enzymatic activity and an inactive variant thereof. The art does not allow the predictability of function based on the structure.

Thus, a conservatively substituted amino acid variant of a polypeptide having ability to oxidize a retinoid, hydroxylate a retinoid at the 4-position of the β-ionone ring or a polypeptide that binds to the specific antibody and has no specific function, lack sufficient written description needed to practice the invention of claims 83-106.

Claims 83, 86-90 and 93-106 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a all-*trans* retinoic acid 4-hydroxylase encoded by SEQ ID NOs: 3, 5 or 31 or encoded by a sequence that hybridizes thereto under stringent conditions, does not reasonably provide enablement for a conservatively substituted amino acid variant thereof, a retinoid oxidase of any substrate specificity that is encoded by a sequence that hybridizes to SEQ ID NOs: 3, 5 or 31 and a conservatively substituted amino acid variant thereof as well as a polypeptide of unknown function that binds to an antibody specific for SEQ ID NOs: 3, 5 or 31. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are broader than the enablement provided by the disclosure with regard to the huge number of all possible derivatives having the desired enzymatic activities.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Factors pertinent to this discussion include predictability of the art, guidance in the specification, breadth of claims, and the amount of experimentation that would be necessary to use the invention.

Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claim, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any sequence that is claimed in claims 83-90 because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting the requisite activity. With regard to claims 83-90, the specification does not teach the structure that is responsible for a specific all-*trans* retinoic acid 4-hydroxylase activity as compared to any other retinoid oxidizing activity;(B) the general tolerance of a protein to modification and extent of such tolerance; © a rational and predictable scheme for modifying any amino acid residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including a number of amino acid modifications of SEQ ID NOs: 2, 4 or 32. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of a protein having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

Claims 96-106 are drawn to proteins with no function. Applicants have not provided sufficient guidance as to what is the function of proteins encompassed by the claims.

The state of the art does not allow the predictability of the properties based on the structure. Therefore, one skilled in the art would require guidance as to how to use a polypeptide of unknown function that binds to an antibody specific for SEQ ID NOs: 2, 4 or 32 in a manner reasonably correlated with the scope of the claims. Without such guidance, the experimentation left to those skilled in the art is undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 83-95 and 103-106 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 83-95 and 103-106 recite "conservatively substituted amino acid variant thereof". There are no clear assigned definitions of the term "conservatively substituted amino acid variant" in the art. In claims 83-95 it is further unclear whether said variant should retain the requisite enzymatic activity.

Furthermore, the claims are confusing because the recitation of "including" renders the Markush group improper.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 96-106 are rejected under 35 U.S.C. 102(b) as being anticipated by Vetter et al.

Vetter et al. teach the amino acid sequence of an inducible cytochrome P-450 protein from Periwinkle (*Catharanthus roseus* L.) (page 1002, Figure 3.). this

polypeptide will bind to an antibody specific for SEQ ID NOs: 3, 5 or 31 and, therefore anticipates claims 96-106.

Shen et al. teach the amino acid sequence of a mouse cytochrome P-450 protein (page 11485, Figure 3.). this polypeptide will bind to an antibody specific for SEQ ID NOs: 3, 5 or 31 and, therefore anticipates claims 96-106.

Double Patenting

Applicant is advised that should claims 84 and 85 be found allowable, claims 91 and 92 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Polypeptides of the same structure inherently have the same function.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky whose telephone number is (703) 306-3222. The examiner can normally be reached Monday through Friday from 9:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX phone number for Technology Center 1600 is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Center receptionist whose telephone number is (703) 308-0196.

Elizabeth Slobodyansky, PhD
Primary Examiner

November 2, 2001